

Amendments to th Specification

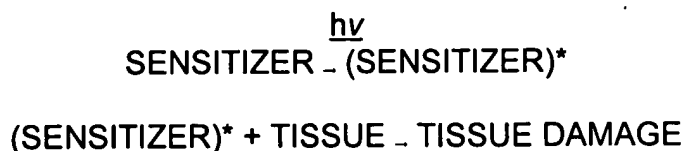
Please replace the paragraph on page 2, beginning with line 3 through line 18 with the following rewritten paragraph -

Phototherapy has been in existence for many centuries and has been used to treat various skin surface ailments. As early as 1400 B.C. in India, plant extracts (psoralens), in combination with sunlight, were used to treat vitiligo. In 1903, Von Tappeiner and Jesionek[[,]] used eosin as a photosensitizer for treating skin cancer, lupus of the skin, and condylomata of female genitalia. Over the years, the combination of psoralens and ultraviolet A (low-energy) radiation has been used to treat a wide variety of dermatological diseases and manifestations including psoriasis, parapsoriasis, cutaneous T-cell lymphoma, eczema, vitiligo, areata, and neonatal bilirubinemia. Although the potential of cancer phototherapy has been recognized since the early 1900's, systematic studies to demonstrate safety and efficacy began only in 1967 with the treatment of breast carcinoma. In 1975, Dougherty et al. conclusively established that long-term cure is possible with photodynamic therapy (PDT). Currently, phototherapeutic methods are also being investigated for the treatment of some cardiovascular disorders such as atherosclerosis and vascular restenosis, for the treatment of rheumatoid arthritis, and for the treatment of some inflammatory diseases such as Chron's disease.

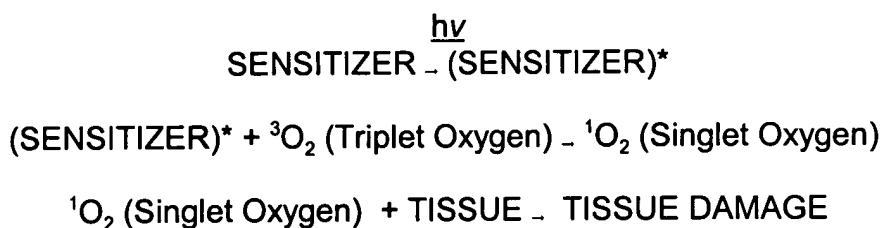
Please replace the paragraph on page 3, beginning with line 9 through line 20 with the following rewritten paragraph -

Photosensitizers operate via two distinct mechanisms, termed Types 1

and 2. The type 1 mechanism is shown in the following scheme:



Type 1 mechanisms involve direct energy or electron transfer from the photosensitizer to the cellular components thereby causing cell death. Type 2 mechanisms involve two distinct steps, as shown in the following scheme:



Please replace the paragraph on page 6, beginning with line 4 through page 7 line 2 with the following rewritten paragraph -

The present invention discloses novel compounds including organic azides for phototherapy of tumors and other lesions. More specifically, the present invention discloses compounds having the formula



wherein DYE is an aromatic or a heteroaromatic radical derived from the group consisting of cyanines, indocyanines, phthalocyanines, rhodamines, phenoxazines, phenothiazines, phenoselenazines, fluoresceins, porphyrins, benzoporphyrins, squaraines, corrins, croconiums, azo dyes, methine dyes, and indolenium dyes. E is selected from the group consisting of somatostatin receptor binding molecules, heat

sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholecystekinin receptor binding molecules, steroid receptor binding molecules, and carbohydrate receptor binding molecules. L is selected from the group consisting of $-(CH_2)_a-$, $-(CH_2)_bCONR^1-$, $-N(R^2)CO(CH_2)_c-$, $-OCO(CH_2)_d-$, $-(CH_2)_eCO_2-$, $-OCONH-$, $-OCO_2-$, $-HNCONH-$, $-HNCSNH-$, $-HNNHCO-$, $-OSO_2-$, $-NR^3(CH_2)_fCONR^4-$, $-CONR^5(CH_2)_gNR^6CO-$, and $-NR^7CO(CH_2)_hCONR^8-$. X is either a single bond or is selected from the group consisting of $-(CH_2)_i-$, $-OCO-$, $-HNCO-$, $-(CH_2)_jCO-$, and $-(CH_2)_kOCO-$. R^1 to R^8 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, $-OH$, C1-C10 polyhydroxyalkyl, C1-C10 alkoxy, C1-C10 alkoxyalkyl, $-SO_3H$, $-(CH_2)_lCO_2H$, and $-(CH_2)_mNR^9R^{10}$. R^9 and R^{10} are independently selected from the group consisting of hydrogen, C1-C10 alkyl, C5-C10 aryl, and C1-C10 polyhydroxyalkyl. And a to l independently range from 0 to 10.

Please replace the paragraph on page 7, beginning with line 3 through page 8 line 4 with the following rewritten paragraph -

The present invention also discloses a method of performing a therapeutic procedure using the compounds of the present invention. An effective amount of organic azide photosensitizer having the formula



is administered to a subject. In this formula, DYE is an aromatic or a heteroaromatic radical derived from the group consisting of cyanines, indocyanines, phthalocyanines, rhodamines, phenoxazines, phenothiazines, phenoselenazines, fluoresceins,

porphyrins, benzoporphyrins, squaraines, corrins, croconiums, azo dyes, methine dyes, and indolenium dyes. E is a hydrogen atom or is selected from the group consisting of somatostatin receptor binding molecules, heat sensitive bacterioendotoxin receptor binding molecules, neurotensin receptor binding molecules, bombesin receptor binding molecules, cholecystekinin receptor binding molecules, steroid receptor binding molecules, and carbohydrate receptor binding molecules. L is selected from the group consisting of $-(CH_2)_a-$, $-(CH_2)_bCONR^1-$, $-N(R^2)CO(CH_2)_c-$, $-OCO(CH_2)_d-$, $-(CH_2)_eCO_2-$, $-OCONH-$, $-OCO_2-$, $-HNCONH-$, $-HNCSNH-$, $-HNNHCO-$, $-OSO_2-$, $-NR^3(CH_2)_eCONR^4-$, $-CONR^5(CH_2)_fNR^6CO-$, and $-NR^7CO(CH_2)_gCONR^8-$. X is either a single bond or is selected from the group consisting of $-(CH_2)_h-$, $-OCO-$, $-HNCO-$, $-(CH_2)_iCO-$, and $-(CH_2)_jOCO-$. R^1 to R^8 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, -OH, C1-C10 polyhydroxyalkyl, C1-C10 alkoxy, C1-C10 alkoxyalkyl, $-SO_3H$, $-(CH_2)_kCO_2H$, and $-(CH_2)_lNR^9R^{10}$. R^9 and R^{10} are independently selected from the group consisting of hydrogen, C1-C10 alkyl, C5-C10 aryl, and C1-C10 polyhydroxyalkyl. And a to l independently range from 0 to 10. Following administration, the photosensitizer is allowed to accumulate in target tissue which is exposed to a light of wavelength between 300 and 950 nm. This light has sufficient power and fluence rate to cause necrosis or apoptosis of the said target tissue.

Please replace the paragraphs on page 8, beginning with line 5 through page 9, line 2 with the following rewritten paragraphs -

In an alternative embodiment of the method of the present invention, the

compounds of the present invention may be used to perform a phototherapeutic procedure including the following steps. A homogeneous photosensitizing mixture consisting of two or more Type 1 agents is prepared. This photosensitizing mixture is allowed to accumulate in target tissue which is exposed to a light of wavelength between 300 and 950 nm with sufficient power and fluence rate to cause necrosis or apoptosis of the target tissue.

In another alternative embodiment of the method of the present invention, the compounds of the present invention may be used to perform a phototherapeutic procedure including the following steps. A homogeneous photosensitizing mixture consisting of two or more Type 2 (PDT) agents is prepared. This photosensitizing mixture is allowed to accumulate in target tissue which is exposed to light of wavelength between 300 and 950 nm with sufficient power and fluence rate to cause necrosis or apoptosis of the target tissue.

In a further alternative embodiment of the method of the present invention, the compounds of the present invention may be used to perform a phototherapeutic procedure including the following steps. A heterogeneous photosensitizing mixture consisting of one or more Type 1 agents and one or more Type 2 agents is prepared. This photosensitizing mixture is allowed to accumulate in target tissue which is exposed to light of wavelength between 300 and 950 nm with sufficient power and influence rate to cause necrosis or apoptosis of ~~said~~ the target tissue.

Please replace the paragraph on page 11, beginning with line 1 through

line 12 with the following rewritten paragraph -

In an alternative embodiment, azides according to the present invention have the general formula 1 above wherein DYE is an aromatic or a heteroaromatic radical derived from the group consisting of cyanines, phthalocyanines, rhodamines, porphyrins, benzoporphyrins, and corrins; E is selected from the group consisting of octreotide and octreotate peptides, heat-sensitive bacterioendotoxin receptor binding peptides, carcinoembryonic antigen antibody (anti-CEA), bombesin receptor binding peptide, neurotensin receptor binding peptide, cholecystekinin receptor binding peptide, and estrogen steroids; L is selected from the group consisting of -HNCO- , $\text{-CONR}^1\text{-}$, -HNCSNH- , -HNNHCO- , $\text{-(CH}_2\text{)}_a\text{CONR}^1\text{-}$, $\text{-CONR}^1\text{(CH}_2\text{)}_a\text{NR}^2\text{CO-}$, and R^1 and R^2 are independently selected from the group consisting of hydrogen, C1-C10 alkyl, C1-C5 polyhydroxyalkyl; and a, b, and c independently range from 0 to 6.

Please replace the paragraph on page 11, beginning with line 13 through line 25 with the following rewritten paragraph -

These compounds operate by a dual mechanism as shown in Fig. 1. N_3 is the azide moiety that produces nitrene upon photoactivation and DYE is an aromatic chromophore that undergoes photosensitization and produces singlet oxygen for PDT. Aliphatic azido compounds can also be used for phototherapy, but may require high-energy light for activation unless the azide moiety is attached to a conjugated polyene system. L is a linker between the chromophore and the epitope. Epitope (E) is a particular region of the molecule that is recognized by, and binds to, the target site on the cell. An epitope is usually, but not always, associated with

biomolecules, which includes hormones, amino acids, peptides, peptidomimetics, proteins, nucleosides, nucleotides, nucleic acids, enzymes, carbohydrates, glycomimetics, lipids, albumins, mono- and polyclonal antibodies, receptors, inclusion compounds such as cyclodextrins, and receptor binding molecules. Specific examples of biomolecules include steroid hormones for the treatment of breast and prostate lesions, somatostatin, bombesin, and neurotensin receptor binding molecules for the treatment of neuroendocrine tumors, cholecystekinin (CCK) receptor binding molecules for the treatment of lung cancer, heat sensitive bacterioendotoxin (ST) receptor and carcinoembryonic antigen (CEA) binding molecules for the treatment of colorectal cancer, dihydroxyindolecarboxylic acid and other melanin producing biosynthetic intermediates for melanoma, integrin receptor and atheroscleratic plaque binding molecules for the treatment of vascular diseases, and amyloid plaque binding molecules for the treatment of brain lesions. Biomolecules for use in the present invention may also include synthetic polymers. Examples of synthetic polymers include polyaminoacids, polyols, polyamines, polyacids, oligonucleotides, arborols, dendrimers, and aptamers. Coupling of diagnostic and radiotherapeutic agents to biomolecules can be accomplished by methods well known in the art, as disclosed in Hnatowich et al., *Radioactive Labeling of Antibody: A simple and efficient method*. Science, 1983, 220, 613-615; A. Pelegrin et al., *Photoimmunodiagnosis with antibody-fluorescein conjugates: in vitro and in vivo preclinical studies*. Journal of Cellular Pharmacology, 1992, 3, 141-145; and U.S. Patent No. 5,714,342, each of which is expressly incorporated by reference herein in its entirety. Successful specific targeting of fluorescent dyes to tumors using antibodies and peptides for diagnostic imaging of

tumors has been demonstrated by us and others, for example, in S.A. Achilefu et al., *Novel receptor-targeted fluorescent contrast agents for in vivo tumor imaging*, Investigative Radiology, 2000, 35(8), 479-485; B. Ballou et al., *Tumor labeling in vivo using cyanine-conjugated monoclonal antibodies*. Cancer Immunology and Immunotherapy, 1995, 41, 257-263; and K. Licha et al., *New contrast agents for optical imaging: acid-cleavable conjugates of cyanine dyes with biomolecules*. In Biomedical Imaging: Reporters, Dyes, and Instrumentation, D.J. Bornhop, C. Contag, and E.M. Sevick-Muraca (Eds.), Proceedings of SPIE, 1999, 3600, 29-35, each of which is expressly incorporated by reference herein in its entirety. Therefore, the inventive receptor-targeted phototherapeutic agents are expected to be effective in the treatment of various lesions.

Please replace the paragraph on page 13, beginning with line 7 through line 16 with the following rewritten paragraph -

In the present invention, dual phototherapeutic effect involving both Type 1 and Type 2 mechanisms can be accomplished by incorporating the reactive intermediate precursors into a conventional PDT ~~dyes~~ dye and using a dual wavelength light source to effect the generation of reactive intermediates as well as the generation of singlet oxygen. In some cases it may be possible to activate both Type 1 and Type 2 mechanisms using same wavelength of light. Dyes containing azide group have been prepared previously, as in S. Sunthakar et al., *Reactive disperse dyes. 1. Reactivity involving nitrene intermediate from azido group*. Indian Journal of Chemistry, 1973,

11(5), 503-504, which is expressly incorporated by reference herein in its entirety.

Please replace the paragraph on page 13, beginning with line 17 through line 21 with the following rewritten paragraph -

In the process outlined in Fig. 1, the photoexcitation of the aromatic chromophore effects rapid intramolecular energy transfer to the azido group, resulting in bond rupture and production of nitrene and molecular nitrogen. The nitrogen that is released is in a vibrationally excited state, which may cause additional cellular injury.